REMARKS

A. Status of the Claims

Claims 34-35, 39-40, 42, 45, 48, 54, 58-69, 71-73, and 75-76 were pending at the time of the Action. Claims 42, 45, 54, 58, 59, 63, 66-69, 71, and 75 have been withdrawn from consideration as being drawn to non-elected inventions or species. Claim 34 has been amended to recite only the three peptides (i.e., SEQ ID NOs: 60, 63, and 17) elected in Applicant's response to the restriction requirement, which was filed on October 26, 2007. In view of the amendment to claim 34, claims 39, 40, 42, 45, 48, 54, 67, and 68 have also been amended and claims 35, 60-62, and 64-66 have been canceled. Thus, claims 34, 39-40, 42, 45, 48, 54, 58-59, 63, 67-69, 71-73, and 75-76 are now pending.

B. Objections to the Specification

The specification and sequence listing have been amended to address objections noted in items 6 and 7 on page 3 of the Action. The withdrawal of these objections is requested.

C. The Claims Are Enabled

The Action rejects claims 34, 35, 39, 40, 48, 60-62, 64, 65, 72, and 73 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Although the Examiner acknowledges that the disclosed peptides are capable of inducing T-cell responses, the Examiner argues that this is insufficient to establish their effectiveness in an HCV vaccine. Applicant traverses this rejection.

The Examiner's primary focus in making the present enablement rejection is the lack of predictability in achieving a therapeutic benefit against HCV infection. In support of this argument, the Examiner cites several references describing the lack of success in developing HCV vaccines to date. While the level of predictability is one factor to consider when determining whether a disclosure satisfies the enablement requirement, it is not the only factor.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). The Examiner's analysis must consider all the evidence related to each of the *Wands* factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands*, 858 F.2d at 737, 740. For the reasons set forth below, the evidence as a whole demonstrates that the current claims are enabled.

1. The Human Clinical Trial Disclosed in the Specification

Example VII of the present specification discloses a human clinical study demonstrating that T-cell immunogenicity resulted from an HCV vaccine dose optimization trial. The HCV vaccine used in this clinical trial comprised HCV peptides Ipep 89, Ipep 84, and Ipep 1426, which correspond to SEQ ID NOs: 17, 60, and 63, respectively. Accordingly, this is an HCV vaccine encompassed by the current claims.

Before a drug can enter human clinical trials, the sponsor must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Accordingly, the MPEP states that: ***"as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility."*** MPEP § 2107.03.[1]

The Action does not mention Applicant's human clinical data nor does it provide any argument explaining why the Examiner's evidence would be sufficient to overcome the presumption that the subject matter of this clinical trial is reasonably predictive of having the asserted therapeutic utility.

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[1] Although MPEP § 2107.03 is primarily concerned with the utility requirement of 35 U.S.C. § 101, lack of enablement under § 112, ¶ 1, and absence of utility under § 101 are closely related grounds of unpatentability. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1358 (Fed. Cir. 1999). This is because the how-to-use prong of § 112, incorporates as a matter of law the requirement of § 101 that the specification disclose as a matter of fact a practical utility for the invention. *See In re Ziegler*, 992 F.2d 1197, 1200 (Fed. Cir. 1993). When the issue of whether data from human clinical trials is required for the patentability is raised in the context of the enablement requirement under § 112, the Federal Circuit has focused its analysis on the "utility" of the invention. *See e.g., In re Brana*, 51 F.3d 1560, (Fed. Cir. 1995).

2. *Demonstrating Efficacy in Human Clinical Trials Is Not a Requirement for Patentability*

Demonstrating therapeutic efficacy in human clinical trials is not a requirement for patentability. *In re Brana,* 51 F.3d 1560, 1568 (Fed. Cir. 1995). Yet this appears to be the standard to which the Examiner is holding the present application. The Examiner is reminded that the stage at which an invention in the pharmaceutical field becomes useful is well before it is ready to be administered to humans; and confirming the full safety and effectiveness of a particular drug for human use is the responsibility of the Food and Drug Administration (FDA), not the Patent Office. *See Id.* at 1567-8.

Moreover, because the initial burden is on the Examiner to give reasons for the lack of enablement, the Examiner must also give reasons for a conclusion of lack of correlation for the *in vitro* and *in vivo* assays in the present specification and the claimed invention. MPEP § 2164.02. A rigorous or an invariable exact correlation is not required. *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985). The Examiner has not satisfied this burden.

For example, the present specification discloses a working example of an *in vivo* human clinical study demonstrating that T-cell immunogenicity resulted from an HCV vaccine dose optimization trial (Example VII). In this study, vaccine-induced T-cell immune responses in the subjects served as surrogate parameters of efficacy (Example VII, p. 50, first paragraph, as numbered in the substitute specification). The Examiner fails to establish a lack of correlation between this study and the claimed invention.

3. *The Klade Declaration*

Applicant submits the declaration of Dr. Christophe Klade under 37 C.F.R. § 1.132 (the "Klade Declaration," attached as Exhibit 1), as further evidence that the current claims are enabled. Dr. Klade is named as an inventor of the present patent application and is employed by Intercell AG, which is the assignee of the present application. The Klade Declaration presents

data from additional clinical trials, which were published in Firbas *et al.*, "Immunogenicity and safety of a novel therapeutic hepatitis C virus (HCV) peptide vaccine: A randomized, placebo controlled trial for dose optimization in 128 healthy subjects," *Vaccine*, 24:4343-4353 (2006).

The Klade Declaration and Firbas *et al.* describe a clinical study of an HCV vaccine called IC41 in 128 HLA A2 positive healthy humans. IC41 contains the following HCV peptides: Ipep 83, Ipep 84, Ipep 87, Ipep 89, and Ipep 1426 (Klade Declaration, para. 5). These peptides correspond to SEQ ID NOs: 72, 60, 19, 17, and 63, respectively, of the present application (Klade Declaration, para. 5). Thus, IC41 is a vaccine encompassed by the current claims. In addition to the HCV epitopes, the IC41 vaccine also contains poly-L-arginine as an adjuvant (Klade Declaration, para. 5). The IC41 vaccine was prepared in a similar manner to the compositions described in the present application (Klade Declaration, para. 5, citing Firbas *et al.* at 4344, col. 2; Application Serial No. 10/564,429, Examples I and V).

Immunization with IC41 was found to be safe and well tolerated (Klade Declaration, para. 7). The immunogenicity of the IC41 vaccine was measured using interferon-gamma ELIspot assays, T cell Proliferation assays, and HLA tetramer-binding assays on cryopreserved PBMCs (Klade Declaration, pare 8). These assays allow reliable measurements of epitope-specific T cell responses induced by IC41 and serve as surrogate parameters of efficacy (Klade Declaration, para. 8). The efficacy results of the IC41 HCV vaccine were positive as confirmed by the HCV peptide specific T cell proliferation, which increased with the number of vaccinations and peaked after the last vaccination (Klade Declaration, para. 9).

The Klade Declaration summarizes that at least three conclusions can be drawn from the IC41 HCV vaccine studies described in Firbas *et al.*: (1) the IC41 HCV vaccine was generally safe and well tolerated; (2) the IC41 HCV vaccine/poly-L-arginine combination provokes a T-cell immune response in humans, and such a response serves as a surrogate parameter of

efficacy; and (3) the data confirms the existence of a synergistic effect with co-administration of the IC41 HCV vaccine and poly-L-arginine enhances the induction of functional IFN-γ secreting T cells in humans (Klade Declaration, para. 10).

4. The Wedemeyer Declaration

As further evidence that the current claims are enabled, Applicant submits the declaration of Dr. Hans Heinrich Wedemeyer under 37 C.F.R. § 1.132 (the "Wedemeyer Declaration," attached as Exhibit 2). Dr. Wedemeyer is a medical doctor with the Department of Gastroenterology and Hepatology at Medizinische Hochschule, located in Hannover, Germany. He is a member of a research group conducting Phase II clinical trials for the IC41 HCV vaccine at Medizinische Hochschule. The IC41 vaccine described in the Wedemeyer Declaration is the same IC41 vaccine described in the Klade Declaration and the Firbas *et al.* publication (*see* Wedemeyer Declaration, para. 4). Thus, the Wedemeyer Declaration is describing a vaccine encompassed by the current claims.

The phase II clinical trial involves 50 human patients with chronic hepatitis C, genotype 1, naïve to treatment and positive for HLA-A2 (Wedemeyer Declaration, para. 6). These patients received 8 intra dermal vaccinations of IC41 (*i.e.*, 2.5 mg/ml peptides adjuvanted with 2 mg/ml poly-L-arginine) in bi-weekly intervals (Wedemeyer Declaration, para. 6). Therapeutic efficacy of IC41 vaccination was assessed by quantifying each patient's viral load by measuring HCV RNA levels prior to receiving any IC41 vaccination (baseline) and prior to each subsequent IC41 vaccination (Wedemeyer Declaration, para. 7). Follow up HCV RNA quantifications were performed two weeks and twenty-four weeks after the last IC41 vaccination (Wedemeyer Declaration, para. 7).

The IC41 vaccinations resulted in a statistically significant decline of HCV RNA load in 92% of the patients by week 12 (Wedemeyer Declaration, para. 7). A statistically significant

decline in HCV RNA can be seen at week 8 when the data from high viral load (> 2000000 U/mL) patients were analyzed separately (Wedemeyer Declaration, para. 7). The Wedemeyer Declaration concluded that such a reduction in HCV RNA load in patients equates to a therapeutically effective response from the IC41 vaccine (Wedemeyer Declaration, para. 7).

5. Summary

The Examiner acknowledges that the disclosed peptides are capable of inducing T-cell responses. Thus, the Examiner's only issue with enablement appears to be with establishing the degree of efficacy of the claimed HCV vaccine. For at least the reasons described above, the present specification satisfies the enablement requirement of 35 U.S.C. § 112, first paragraph, in this regard.

First, the present specification discloses a human clinical trial on a HCV vaccine and, in regard to such clinical trials, the MPEP states that: "as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility." MPEP § 2107.03. The Action has not overcome this presumption.

Second, it is the Examiner's burden to give reasons for a conclusion of lack of correlation for the *in vitro* and *in vivo* assays in the present specification and the claimed invention. MPEP § 2164.02. The present specification teaches that vaccine-induced T-cell immune responses in the human subjects treated with the HCV vaccine served as surrogate parameters of efficacy. The Examiner has not satisfied this burden because the Examiner has not established any lack of correlation between vaccine-induced T-cell immune responses and efficacy. Rather, the Examiner has merely noted the failures of others to achieve therapeutic treatments against HCV

infection. While this may reflect the state of the prior art, it does not establish a lack of correlation between the *in vivo* assays in the present specification and the claimed invention.

Third, demonstrating therapeutic efficacy in human clinical trials is not a requirement for patentability. *In re Brana,* 51 F.3d 1560, 1568 (Fed. Cir. 1995). Yet this appears to be the standard to which the Examiner is holding the present application.

Fourth, the Klade and Wedemeyer Declarations provide further evidence that the claims were enabled at the time of filing by providing additional data from human clinical trials on an HCV vaccine according to the teachings of the specification and the current claims.

In view of the above, Applicant, requests the withdrawal of this rejection.

D. The Claims Are Patentable Over the Cited References

1. Wentworth

Claims 34, 35, 39, and 40 are rejected under 35 U.S.C. § 103(a) as being obvious over Wentworth *et al.* (Int. Immunol., 8:651-659 (1996)) (IDS ref. C83). Wentworth is said to disclose three epitopes found in the hotspot epitopes of SEQ ID NOs: 73, 26, and 126 of claim 34, and include the epitopes of SEQ ID NOs: 146 and 85 of claim 39. The Action also alleges that Wentworth discloses epitopes found in SEQ ID NOs: 73, 26, and 63.

Current claim 34 is directed to a hepatitis C virus (HCV) vaccine comprising at least an epitope from each of the following peptides: GYKVLVLNPSVAAT (SEQ ID NO:60), HMWNFISGIQYLAGLSTLPGNPA (SEQ ID NO:63), and CINGVCWTV (SEQ ID NO:17). The Action does not allege that the combination of SEQ ID NOs: 60, 17, and 63 is obvious over Wentworth. Thus, a *prima facie* case of obviousness has not been established against the current claims. Applicant, therefore, requests the withdrawal of this rejection.

2. *Diepolder, Cerny, and Lamonaca*

Claims 34, 35, 39, 40, 48, 60, 62, and 64 are rejected under 35 U.S.C. § 103(a) as being obvious over Diepolder *et al.*, (J. Virol., 71:6011-19 (1997)), Cerny *et al.* (J. Clin. Invest., 95:521-30 (1995)), and Lamonaca (Hepatology, 30:1088-98 (1999)). Diepolder is said to teach an epitope corresponding to SEQ ID NO: 60, Cerny is said to teach an epitope corresponding to SEQ ID NO: 17, and Lamonaca is said to teach an epitope corresponding to SEQ ID NO: 63. The Action alleges that it would have been obvious to combine these epitopes to induce an immune response since each reference teaches that the epitopes are anti-HCV T-cell epitopes. Applicant traverses this rejection.

Current, independent claim 34 is directed to a hepatitis C virus (HCV) vaccine comprising at least an epitope from each of the following peptides: GYKVLVLNPSVAAT (SEQ ID NO:60), HMWNFISGIQYLAGLSTLPGNPA (SEQ ID NO:63), and CINGVCWTV (SEQ ID NO:17). None of the references cited in the rejection disclose a HCV vaccine or show that their disclosed peptides can be administered to a patient to stimulate an immune response in the patient. In addition, none of the references suggest the particular combination of epitopes recited in the current claims.

The Supreme Court stated in *KSR*, that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct. 1727, 1741 (2007). The Examiner still must provide an apparent reason to combine the elements in the fashion claimed by the Applicant. *Id.* Additionally, the Supreme Court noted that when the combined elements work together in an unexpected and fruitful manner, this is evidence that the combination was not obvious. *Id.* at 1740.

Vaccines encompassed by claim 34 have been and continue to be the subject of human clinical trials (*see* Specification, Example VII; Klade Declaration; Wedemeyer Declaration).

This success could not have been predicted from the teachings of Diepolder, Cerny, and Lamonaca. As the Examiner is well aware, years of research by others have failed to produce a HCV vaccine that is approved for human use (*see* Action, p. 5). Accordingly, the *in vitro* studies of Diepolder, Cerny, and Lamonaca could not have provided a person of ordinary skill in the art of a reasonable expectation of success. Moreover, the failure of other to develop a HCV vaccine despite the long-felt need for such a vaccine is further evidence of the non-obviousness of the present claims (*see* MPEP § 2141, stating that Office personnel must consider objective evidence, sometimes referred to as "secondary considerations," which may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results).

In view of the above, the current claims are patentable over Diepolder, Cerny, and Lamonaca. Applicant, therefore, requests the withdrawal of this rejection.

3. The Obviousness Rejections Against Various Dependent Claims

The Action also rejects claims 39, 48, 61, 64, and 65 under 35 U.S.C. § 103(a) as being obvious over Diepolder, Cerny, Lamonaca, in view of Wentworth, Day *et al.* (J. Virol., 76:12584-595 (2002)), Van Der Berg (WO 02/70006), Abrams *et al.* (Cell Immunol., 182:137-51 (1997)), and Chisari *et al.* (U.S. 2002/0115061). Additionally, the Action rejects claims 72 and 73 are rejected under 35 U.S.C. § 103(a) as being obvious over either Wentworth or the combination of Diepolder, Cerny, and Lamonaca, in view of Schmidt *et al.* (WO 01/93905). Applicant traverses.

Independent claim 34 is non-obvious for the reasons discussed in the preceding two sections. If an independent claim is nonobvious under 35 U.S.C. § 103(a), then any claim depending therefrom is nonobvious. MPEP § 2143.03. Claims 39, 48, 61, 64, 65, 72, and 73 all depend directly or indirectly from claim 34. Accordingly, these claims are also non-obvious. Applicant, therefore, requests the withdrawal of these rejections.

E. The Provisional Double-Patenting Rejection

Claims 34, 35, 36, 40, 48, 60-62, 64, and 65 are provisionally rejected for obviousness-type double patenting over co-pending Application No. 11/082,595. A provisional double-patenting rejection is not a final rejection that blocks the prosecution of all of the conflicting applications. If a provisional double-patenting rejection is the only rejection remaining in an application, the Examiner should withdraw the rejection and permit the application to issue as a patent. MPEP § 804(I)(B). After one application issues as a patent, the provisional double-patenting rejection in the remaining application is converted to an actual double patenting rejection. Id. Thus, either the present application or the '595 application must issue as a patent before an actual double patenting rejection may be raised against the remaining application.

F. Conclusion

Applicant believes that this is a full and complete response to the Office Action mailed November 6, 2007. Should the Examiner have any questions, comments, or suggestions relating to this case, the Examiner is invited to contact the undersigned Applicant's representative at (512) 536-5654.

Respectfully submitted,

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